EPIDEMIOLOGY OF ROTAVIRUS DIARRHEA AMONG CHILDREN AGED LESS THAN 5 YEARS IN RURAL SOUTHERN ETHIOPIA

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Abstract. The objective of this study was to determine the epidemiological and clinical features of rotavirus infection among children aged less than 5 years in rural southern Ethiopia. We conducted a hospital-based, prospective study among children aged less than 5 years with acute diarrhea and moderate to severe dehydration attending the outpatient department of Gambo Rural Hospital, Ethiopia during September-November 2012. Three hundred fourteen children were included in the study, of whom 137 (43.6%) had rotavirus infection. The average age of children with rotavirus infection was lower than those without it [odds ratio (OR): 0.94]. Finding severe dehydration on skin pinch test (adjusted OR: 3.76) and having diarrhea for ≤3 days (adjusted OR: 2.50) were associated with rotavirus infection. The mortality rate was 4.4% among rotavirus infection children and 0% among non-rotavirus diarrhea cases (p=0.006). Rotavirus infection should be suspected in children with severe dehydration on a skin pinch test and among those presenting with diarrhea for ≤ 3 days in rural southern Ethiopia.

Keywords: rotavirus, diarrhea, children under five, mortality, low-income country, Ethiopia

INTRODUCTION

Diarrheal diseases in children are a major public health problem in low income countries, including Ethiopia. Mortality estimates in low-income countries reveal 1.3 million deaths in 2008 due to diarrheal illnesses within the first five years of life (Black *et al*, 2010). Tate *et al* (2012) estimated the worldwide rotavirus-associated mortality among children aged less than 5 years in 2008 was 453,000 deaths, 37% of the deaths due to diarrhea and 5% of all deaths in children aged less than 5 years.

The prevalence, serotypes and epidemiology distribution of rotavirus infection have been studied extensively in high

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and middle income developed countries (Fischer *et al*, 2005; Zerr *et al*, 2005; Junaid *et al*, 2011). In low-income countries, where rotavirus infection morbidity and mortality are high, these data are lacking due to few studies having been conducted (Junaid *et al*, 2011; Temu *et al*, 2012). Little research about rotavirus infection in Ethiopia has been conducted (Muhe *et al*, 1986; Yassin *et al*, 2012).

Since rotavirus disease cannot be eliminated by water and sanitation improvements alone (Zerr *et al*, 2005), the development of a safe and effective rotavirus vaccine has been a priority (Ruiz-Palacios *et al*, 2006; Vesikari *et al*, 2006). The World Health Organization (WHO) recommends routine use of rotavirus vaccines in all countries, particularly those with high diarrhea-related mortality among children aged less than 5 years (WHO, 2009). Rotavirus vaccines do not prevent rotavirus diarrhea, but do decrease the severity of the infection and that is the reason for introducing them. A rotavirus vaccine has not yet been introduced into private or public health services in Ethiopia. The WHO recommends countries conduct local surveillance studies prior to introducing new vaccines (WHO, 2009).

This study was performed to understand the epidemiology and clinical features of rotavirus infection at a rural hospital in southern Ethiopia. The results of this study will provide baseline information before an appropriate vaccine is introduced.

MATERIALS AND METHODS

This hospital-based, prospective study was conducted from September to November 2012 at Gambo Rural Hospital (GRH), Gambo (Kore), West Arsi Province, Oromia Region, southern Ethiopia, 245 km from Addis Ababa. GRH serves 11 municipalities ("kebeles") with an estimated population of 100,000 inhabitants. Its altitude is 2,200 meters above sea level. The temperature varies between 13ºC and 30ºC, with monthly rainfall varying from June to October. Subsistence farming and animal husbandry are its residents' major occupations.

Inclusion criteria

Children aged less than five years with acute diarrhea (defined as ≥ 3 loose stools / 24 hours for ≤ 5 days) and moderate to severe dehydration who attended the Under Five (out patient) Clinic at GRH were included in the study. The parents or guardian of the children were informed and an oral or written informed consent was obtained from them. The Gorelick scale was used to assess dehydration. The scale states the presence of two or more of the following four clinical findings indicates at least 5% dehydration: (1) capillary refill >2 seconds, (2) dry mucous membranes, (3) absent tears, (4) general weak appearance (Gorelick *et al*, 1997).

Exclusion criteria

Children aged less than five years with acute diarrhea but with an estimated less than 5% dehydration and children who could not give a stool sample were not included in the study.

Demographic and clinical information

The following information for each patient was obtained using a standardized form: place of residence, age, sex, presence and / or duration of fever, vomiting, weakness and malaise, consistency and frequency of stools, presence of mucus and blood in the stools, duration of diarrhea, urine output and treatment at other clinics or by a local healer.

We recorded the presence or obsence of 10 clinical findings: (1) decreased skin

elasticity, (2) capillary refill > 2 seconds, (3) general appearance, (4) absent tears, (5) abnormal respirations, (6) dry mucous membranes, (7) sunken eyes, (8) abnormal radial pulse, (9) tachycardia (heart rate > 150), and (10) decreased urine output. Watery diarrhea was defined as ≥ 3 watery stools within 24 hours for ≤ 5 days.

The mid upper arm circumference (MUAC) was measured with a tape measure on the left arm of children aged 6 to 59 months; readings were taken to the nearest 0.1 cm. Patient outcomes were only available for those admitted to the hospital. The length of hospitalization was also recorded for each patient.

Specimen collection and laboratory procedures

Stool samples were collected in accordance with WHO guidelines on fecal sample collection. Specimens were sent to the laboratory for analysis the same day; most of the specimens were analyzed within 2 hours of collection. Stool specimens were examined by direct microscopy from smears in saline and Lugol's iodine for detecting parasites (trophozoites, cysts, eggs, and larvae) and red blood cells. The fecal samples were tested for rotavirus following the instructions for the rotavirus enzyme immuno-assay (Rotavirus and Adenovirus kit, Francisco Soria Melguizo, S.A., Madrid, Spain).

Data management

Data were coded, entered into logbooks and then analyzed using SPSS 19.0 for Windows (IBM, Armonk, NY). Patients were divided into age groups. Continuous variables, such as age and days of diarrhea, were represented as medians with interquartile ranges (IQR) unless stated otherwise. The relationships between positive and negative rotavirus results and categorical risk factors were analyzed with the chi-square test. The Mann-Whitney *U* test was used to analyze continuous variables, such as age. The association was calculated using the odds ratio (OR) with a 95% confidence interval (CI). A p-value <0.05 was considered statistically significant. Multivariate logistic regression analysis was used to assess the association between the dependent variable (rotavirus infection) and risk factors using a p-value <0.1 as being significant on univariate analysis.

Ethical considerations

This study was approved by the Institutional Ethics Review Board of GRH and the Ethics Review Committee of the Ethiopian Catholic Secretariat.

RESULTS

Three hundred fourteen patients with moderate to severe diarrhea were included in the study. Sixty-nine percent were aged less than 12 months. The age distribution of children with and without rotavirus infection is shown in Table 1. One hundred thirty-seven of 314 patients (43.6%) had rotavirus infection.

The average age of the rotavirus-positive children was less than the rotavirus-negative children (OR=0.94; 95% CI: 0.91-0.98). Neither fever at home, weakness, nor malaise were related to rotavirus infection. Cough was significantly less frequent in rotavirus-positive children. (Table 2). The median number of days with diarrhea was significantly lower in patients with rotavirus disease than in patients with diarrhea from other causes (p=0.002). All the children with rotavirus infection had watery diarrhea, while only 47.5% of children with the other types of diarrhea (p<0.001) had watery diarrhea. Mucus and blood were rarer in the stools of children with rotavirus infection (0.7%

Table 1
Rotavirus infection distribution by age group.

Age group	Total No. (%)	Rotavirus positive No. (%)	Rotavirus negative No. (%)
< 6 months	57 (18.2)	31 (22.6)	26 (14.7)
6 - <12 months	160 (51.0)	76 (55.6)	84 (47.5)
12 - <24 months	62 (19.7)	25 (18.2)	37 (20.9)
24 - <36 months	26 (8.3)	4 (2.9)	22 (12.4)
36 - <48 months	7 (2.2)	1 (0.7)	6 (3.4)
48 - 60 months	2 (0.6)	0 (0)	2 (1.1)
Total	314 (100)	137 (100)	177 (100)

and 2.2%) than in children with rotavirus-negative stools (33.3% and 23.7%) (p<0.001). However, vomiting was more common among rotavirus-positive cases (94.2%) than among rotavirus-negative cases (83.6%) (p=0.007) (Table 2).

The physical examination results of rotavirus-positive and rotavirus-negative children are shown in Table 3. Children with a rotavirus infection were more likely to be hospitalized with severe dehydration, inability to drink, sunken eyes, severe dehydration on the skin pinch test, absence of tears, a capillary refill > 2 seconds, reduce urinary input, and lethargy than children without rotavirus infection.

None of the rotavirus cases had dual infections with intestinal parasites but 11.9% of children with other types of diarrhea did have them (p<0.001). Red blood cells were seen on microscopy in the feces of 6.6% of those rotavirus infection and 22.5% of those without rotavirus infection (p<0.001).

Eighty-six point one percent of children with rotavirus infection were hospitalized compared to 43.3% of children with other types of diarrhea (Table 3). There was not significant difference in the length of admission among rotavirus-positive and rotavirus negative cases. The mortality rate was 4.4% among children with rotavirus infection and 0% among children without rotavirus infection (p=0.006).

Table 4 shows the multivariate logistic analysis of rotavirus infection and various risk factors with p-values <0.1 on univariate analysis. The only signs and symptoms significantly associated with rotavirus infection were diarrhea for ≤ 3 days (p=0.004) and severe dehydration on the skin pinch test (p=0.014). Absence of tears (p=0.068) and non-mucoid diarrhea p=0.055) were not significantly associated.

DISCUSSION

Acute watery diarrhea can be caused by various pathogens, among which viruses are responsible for more than half of the cases. In our study 43.7% of stools were rotavirus-positive. These findings are higher than some studies from Africa where the rates range from 20% to 30% (Moyo *et al*, 2007; Mwenda *et al*, 2010; Temu *et al*, 2012), but are similar to a study from Ghana (Waggie *et al*, 2010) and some inpatient studies from developed countries where nearly half the acute diarrheal cases were rotavirus-positive

Table 2
Age, sex, symptoms, and aspects of stools in rotavirus-positive and rotavirus-negative children.

	Rotavirus positive (n = 137) No. (%)	Rotavirus negative (n = 177) No. (%)	p-value	OR (95% CI)
Median of age in months, (IQR)	8.0 (6-11)	9 (6-14.2)	0.001	0.94 (0.91-0.98)
Age			0.002	
≥12 months	30 (21.9)	67 (37.9)		1
<12 months	107 (78.1)	110 (62.1)		2.17 (1.31-3.60)
Sex			0.62	
Female	63 (46.0)	87 (49.2)		1
Male	74 (54.0)	89 (50.3)		1.15 (0.73-1.80)
Fever at home			0.52	
No	36 (26.3)	49 (27.7)		1
Yes	128 (72.3)	101 (73.7)		1.07 (0.65-1.78)
Weakness			0.15	
No	6 (4.4)	2 (1.1)		1
Yes	131 (95.6)	175 (98.9)		0.25 (0.05-1.26)
Malaise			0.15	
No	6 (4.4)	2 (1.1)		1
Yes	131 (95.6)	175 (98.9)		0.25 (0.05-1.26)
Cough			<0.001	
No	103 (75.2)	89 (50.3)		1
Yes	34 (24.8)	88 (49.7)		0.33 (0.21-0.54)
Vomiting			0.007	
No	8 (5.8)	29 (16.4)		1
Yes	129 (94.2)	148 (83.6)		3.16 (1.39-7.16)
Median number of days with diarrhea at hospital visit (IQR)	3 (2-5)	5 (3-7)	0.002	0.92 (0.88-0.97)
Days of diarrhea			<0.001	
≤3 days	86 (62.8)	54 (30.5)		1
>3 days	51 (37.2)	123 (69.5)		3.84 (2.39-6.15)
Watery diarrhea			<0.001	
No	0 (0)	54 (30.5)		
Yes	137 (100)	123 (47.5)		NA
Blood in feces			<0.001	
No	134 (97.8)	135 (76.3)		1
Yes	3 (2.2)	42 (23.7)		0.07 (0.22-0.24)
Mucus in feces			<0.001	
No	136 (99.3)	118 (66.7)		1
Yes	1 (0.7)	59 (33.3)		0.02 (0.02-0.18)
Previous treatment			<0.001	
No	120 (72.3)	128 (87.6)		1
Yes	17 (27.7)	49 (12.4)		2.70 (1.47-4.95)
Decreased urine output			<0.001	
No	33 (24.1)	111 (63.1)		1
Yes	104 (75.9)	65 (36.9)		5.38 (3.27-8.84)

IQR, interquartile range; OR, odds ratio; CI, confidence interval; NA, not available.

Table 3
Physical examination, laboratory results and outcomes of rotavirus-positive and rotavirus-negative children.

	Rotavirus positive (n = 137) No. (%)	Rotavirus negative (n = 177) No. (%)	p-value	OR (95% CI)
Physical examination				
Dehydration			<0.001	
Moderate	38 (27.7)	137 (77.4)		1
Severe	99 (72.3)	40 (22.6)		8.92 (5.34-14.91)
Lethargy			<0.001	
No	66 (48.2)	148 (83.6)		1
Yes	71 (51.8)	29 (16.4)		5.49 (3.26-9.24)
Restlessness			<0.001	
No	71 (51.8)	29 (16.5)		1
Yes	66 (48.2)	148 (83.6)		0.18 (0.11-0.31)
Sunken eyes			<0.001	
No	10 (7.3)	64 (36.2)		1
Yes	127 (92.7)	113 (63.8)		7.19 (3.53-14.67)
Inability to drink			<0.001	
No	41 (29.9)	136 (76.8)		1
Yes	96 (70.1)	41 (23.2)		7.77 (4.68-12.87)
Oral tolerance to liquids			<0.001	
No	96 (70.1)	39 (22.0)		1
Yes	41 (29.9)	138 (78.0)		0.12 (0.72-0.20)
Severe dehydration on skin pinch test			<0.001	
No	71 (51.8)	155 (87.6)		1
Yes	66 (48.2)	22 (12.4)		6.55 (3.75-11.44)
Absence of tears			<0.001	
No	15 (10.9)	79 (44.6)		1
Yes	122 (89.1)	98 (55.4)		6.55 (3.55-12.09)
Capillary refill > 2 seconds			<0.001	
No	48 (35.0)	134 (75.7)		1
Yes	89 (65.0)	43 (24.3)		5.77 (3.53-9.44)
Gorelick scale			<0.001	
2	3 (2.1)	40 (22.6)		1
3-6	55 (40.1)	106 (59.9)		6.91 (2.05-23.37)
>6	79 (57.1)	31 (17.5)		33.97 (9.78-118)
Mid-upper arm circumference			0.66	
≥ 125 mm	60 (56.1)	87 (59.2)		1
115mm - < 125 mm	28 (26.2)	40 (27.2)		1.02 (0.57-1.82)
<115mm	19 (17.8)	20 (13.6)		1.38 (0.68 - 2.80)
Temperature				
≤ 37.5ºC	105 (76.6)	139 (78.5)		1
>37.5ºC	32 (23.4)	38 (21.5)		1.05 (0.52-2.14)
Laboratory examination				
Stool RBC				
No	128 (93.4)	137 (77.4)	<0.001	1
Yes	9 (6.6)	40 (22.5)		0.24 (0.11-0.52)

Table 3 (Continued).

	Rotavirus positive (n = 137) No. (%)	Rotavirus negative (n = 177) No. (%)	p-value	OR (95% CI)
Adenovirus infection			0.713	
No	133 (97.1)	173 (97.7)		1
Yes	4 (2.9)	4 (2.3)		
Intestinal parasites			<0.001	
No	137 (100)	156 (88.1)		NA
Yes	0 (0)	21 (11.9)		NA
Infection with *Plasmodium falciparum*		0.98		
No	133 (97.1)	176 (99.4)		1
Yes	4 (2.9)	1 (0.6)		0.53 (0.58-47.90)
WBC/μl (n=122)			0.83	1.00 (1.00-1.00)
Median (IQR)	7,350	7,379		
Media (SD)	7,519	7,600		
Outcome				
Admitted to hospital			<0.001	
No	19 (13.9)	99 (56.6)		1
Yes	118 (86.1)	76 (43.3)		8.09 (4.58-14.23)
Days of hospitalization, median (IQR) (n=186)	6 (3-9)	3 (2-6)	0.09	1.04 (0.99-1.08)
Death			0.006	
No	130 (95.6)	176 (100)		
Yes	6 (4.4)	0 (0)		NA

OR, odds ratio; CI, confidence interval; IQR, interquartile range; WBC, white blood cells; RBC, red blood cells; SD, standard deviation; NA, not available.

Table 4
Risk factors for rotavirus infection on multivariate analysis.

	Adjusted OR	95% CI	p-value
≤ 3 days diarrhea	2.50	1.35-4.703	0.004
Severe dehydration on skin pinch test	3.76	1.38-10.23	0.014
Non-mucoid diarrhea	9.43	0.98-75.0	0.055
Absence of tears	2.31	10.98-5.42	0.068
Lethargy	0.42	0.12-1.36	0.14
Vomiting	1.98	0.71-5.49	0.18
Decreased urine output	1.58	0.76-3.26	0.21
Bloody diarrhea	0.39	0.09-1.82	0.23
Sunken eyes	1.15	0.42-3.59	0.78
Age < 12 months	1.07	0.54-2.15	0.83
Capillary refill > 2 seconds	1.13	0.37-3.43	0.83
Cough	0.87	0.44-1.71	0.87
Watery diarrhea	0.02	0.00-	0.99
Tolerance to oral liquid	0.02	0.00-	0.99
Inability to drink	0.02	0.00-	0.99
Severe dehydratation	0.02	0.00-	0.99

OR, odds ratio; CI, confidence interval.

(Forster *et al*, 2009; Enweronu-Laryea *et al*, 2012). These differences could be due to study duration. Our study spanned only three months so the annual prevalence could not be estimated. Our study was conducted during the cool, rainy season. Rotavirus infection is considered a winter disease, with most cases observed in the coldest time of the year.

Our patients' ages ranged from 0 to 59 months, but most were aged less than 12 months, similar to other published studies from low-income countries (Forster *et al*, 2009; Waggie *et al*, 2010; Enweronu-Laryea *et al*, 2012). Most infections in our study occurred in infants, where morbidity and mortality from diarrhea are higher (Tate *et al*, 2012). Symptomatic infection rates decreased with increasing age of the child, similar to other epidemiological studies (Moyo *et al*, 2007; Temu *et al*, 2012). In developed countries the peak incidence of rotavirs infection occurs in older children (Moyo *et al*, 2007; Forster *et al*, 2009; Mwenda *et al*, 2010; Temu *et al*, 2012). The higher prevalence among younger' children in Africa may be explained by a variety of factors, such as unhygienic conditions, nutritional status, avitaminoses, co-infection with other intestinal pathogens or pathogens causing systemic infections, which have not been fully assessed for their relative significance (Forster *et al*, 2009).

In this study, all children with rotavirus infection had watery diarrhea, most without mucus or blood. Vomiting was more common. Only non-mucoid diarrhea was signicicantly associated with rotavirus infection. Vomiting has been reported in other studies associated with rotavirus infection (Waggie *et al*, 2010).

Children with rotavirus infection had a greater risk to come to the hospital with severe dehydration in our study, and have other related symptoms, such as lethargy, sunken eyes, inability to drink, and severe dehydration on a skin pinch test. The two symptoms included in the Gorelick scale associated independently with rotavirus infection were absence of tears and very slow recovery with the skin pinch test (2 seconds). In our study, lethargy and irritability were present in more than half of rotavirus cases.

Hospital admissions were more common among children with rotavirus infection in our study (nearly 90%). The length of hospital stay was slightly longer among children with rotavirus infection. This finding is similar to another study (Temu *et al*, 2012). Diarrhea due to rotavirus infection usually lasts from 4 to 9 days (Guerrant *et al,* 2002; Forster *et al*, 2009; Temu *et al*, 2012).

Our patient outcomes were similar to other studies (Guerrant *et al,* 2002; Forster *et al*, 2009; Temu *et al*, 2012). All the patients in our study with rotavirus infection were treated following Integrated Management of Childhood Illness (IMCI) guidelines; 4.4% of patients died. The risk for death is higher in low-income countries than high-income countries (Tate *et al*, 2012).

Based on the incidence of rotavirus infection over 3 months, we estimated the annual incidence to be about 500 cases. We estimated there are 14,000 children aged less than 5 years living in the catchment area of the hospital; therefore, this represents a prevalence of 357 cases per 10,000 children younger than age 5 years. According to the 2007 population census for Ethiopia by the government, the estimated population of children younger than 5 years living in rural Ethiopia is about 8.6 million. This would give an

estimated 310,000 cases of rotavirus infection per year resulting in 13,000 deaths per year caused by rotavirus infection. This estimate shows the extent of the rotavirus burden in Ehiopia is not negligible.

Our study had the following limitations: stool cultures were not performed; therefore, no information about the bacterial intestinal pathogens could be recovered. Second, socio-demographics were not recorded, so diarrhea in a neighboring child was not studied as an increased risk for rotavirus infection. Third, this study spanned three months, from September to November, so the annual prevalence could not be estimated. Fourth, a major limitation was the lack of virological investigations for G and P genotyping, information that is sorely missing from Ethiopia and urgently needed if the introduction of a universal rotavirus vaccination program is to be considered.

Despite these limitations, we can conclude that rotavirus infection is a major cause of moderate to serve diarrhea in young children, especially among those younger than 12 months. It is common in rural Ethiopia and is accompanied by high morbidity, contributing to longer hospital stays than other types of diarrhea causing moderate to severe dehydration.

This data is important for better understanding the disease before implementing a rotavirus vaccine program, as has been begun in some low-income countries. Rotavirus infection should be suspected in children younger than 12 months with non-mucoid diarrhea, absence of tears, and severe dehydration on a skin pinch test.

ACKNOWLEDGEMENTS

We thank the staff at the Gambo Rural Hospital for their co-operation during this study. Iñaki Alegria was supported by a grant from SEMTSI (Sociedad Española de Medicina Tropical y Salud Internacional), Spain. We express our gratitude to Paul Nordstrom for his assistance with the editing.

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